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PATREA L. PABST
HOLLAND & KNIGHT LLP
SUITE 2000, ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET, N.E.
ATLANTA, GA 30309-3400

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 031704

Application Number: 08/765,324
Filing Date: December 24, 1996
Appellant(s): KOREN ET AL.

Patrea L. Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 29, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

Claims 1-47 been canceled.

This appeal involves claims 48-51.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because it does not reflect the teachings of the specification nor the originally filed claims with respect to the now claimed invention. Appellants discussion of the use of antibodies is not on point to the now claimed invention. Appellants also allege that the method is based on the

discovery that if one removes the lipid (i.e. the instantly claimed delipidation) and denatures the protein (i.e. the instantly claimed reduction and carboxymethylation) then antibodies to the delipidated, denatured protein (or apolipoprotein) will bind to the protein regardless of the amount of lipid present in the lipoprotein form of the apolipoprotein. This characterization of Appellants invention is not articulated in anywhere the specification and is a post filing characterization of a discovery of Appellants which can not be found in any of the passages relied upon by Appellants. There is no conception of the apparently critical nature of the now claimed methodology in the specification or claims as originally filed. The assertion of the nature of the invention lacks written descriptive support in the specification and Appellants have not pointed to the specification by page and line number where Appellants similarly characterizes their invention as such. Appellants also misdirect the issue here and do not specifically point to the specification by page and line number where the instantly claimed discovery can be found. The instantly claimed invention finds support only at page 27, lines 5-16 and page 47, lines 15-34 of the specification and not in the originally filed claims nor is it articulated in the Background of the Invention of the specification. Further, "denaturation" is not art equivalent to (reduction and carboxymethylation) as implied in the summary of the invention in the Appeal Brief. Reduction as applied to proteins is a chemical reduction of any disulfide linkages in a protein and in this case an apolipoprotein and is usually performed with a strong chemical reducing agent. Carboxymethylation is

also chemical reaction that methylates free carboxyl groups. This again is not equivalent to denaturation. Denaturation is defined in the art as a reversible or irreversible loss of function in proteins and nucleic acids resulting form loss of higher order secondary, tertiary or quaternary structure produced by nonphysiological conditions of pH, temperature, salt or organic solvents. Therefore, denaturation is not equivalent to reduction and carboxymethylation, is technically incorrect, does not find support in the specification as filed and Appellants have not provided such a reference. Therefore, reducing agents are not equivalent to denaturing agents and denaturation is not equivalent to the chemical reactions of reduction and carboxymethylation as characterized by Appellants in the Summary of the Invention in the instant Appeal Brief.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The Appellants' statement in the brief that certain claims do not stand or fall together is not agreed with because the issue at hand is the method of for making antibodies to an epitope of a lipoprotein which react with the lipoprotein independently of lipid content and conformation of the lipoprotein by using an immunogen prepared by specifically recited steps in combination with other. The issues with respect to claim 48 are similarly applied to claim 49. The new matter issue of record equally applies to all claims including claim 49 as specifically indicated by the inclusion of the claim 49 in the

rejection of record. There is no separate rejection for monoclonal antibodies and as such, claim 49 has not been separately used as a basis for an appealable rejection by the examiner. Further, Appellants have provided no arguments as to why claim 49 is separately patentable and as such, the claims stand or fall together with respect to the appealed issue.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Lee, D. M. et al, Biochim. Biophys. Acta, 666:133-146, 1981.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 48-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are drawn to a method of making antibodies to an epitope of a lipoprotein which reacts with the lipoprotein independently of lipid content and conformation of the lipoprotein, comprising immunizing an animal with a desired apolipoprotein or lipoprotein which is delipidated, reduced, carboxymethylated and

degraded material has been removed from the delipidated, reduced, carboxymethylated, and solubilized apolipoprotein or lipoprotein. Dependent claims are drawn to monoclonal antibodies and specific lipoproteins or apolipoproteins.

The entire written description support for these method claims are provided for on page 27, lines 5-16 (Example 2) and page 47, lines 15-34. As set forth in Paper Nos. 23, 26, 34 and 37. These passages do not provide for conception and written description support for that which is now broadly claimed because it does not provide conception by way of written description for (a) immunizing with lipoproteins or generic apolipoproteins so treated; (b) antibodies in general/polyclonal antibodies; (c) subgenus of reducing or denaturing agents; (d) immunization of soluble lipoprotein or apolipoprotein produced by the method; and (e) generic means of removal of all self-aggregated and degraded material. As previously set forth in Paper No 34,

The relied upon passages are at pages 27 and 47 of the specification. At page 27 , the specification recites:

> "To obtain an anti-LDL MAb whose binding to LDL particles is not dependent on variations in LDL composition and/or conformation, mice were immunized with soluble ApoB-100 which had been delipidized, reduced, carboxymethylated and, purified by electrophoration in polyacrylamide gels containing 8 M urea (Lee, D. M. et al, Biochim. Biophys. Acta, 666:133-146(1981)). Immunization with such

delipidized, soluble, reduced, carboxymethylated, and electrophoretically purified Apo B-100 has not been previously reported."

At page 47, Example 2 the specification recites:

"The MAb to Apo B, HB3cB3, was produce by immunizing mice with Apo B-100 molecules which had been delipidized, reduced, carboxymethylated and purified by electrophoresis on a polyacrylamide gel containing 8M urea. Delipidized ApoB-100 readily precipitated due to self-aggregation in aqueous media. In addition to self-aggregation, ApoB-100 is also susceptible to fragmentation during the solubilization procedure (Soccorro, L. and Camejo, G. J. Lipid Res., 20:631-645, (1979); Olofsson, S. O. et al., Biochemistry, 19:1059-1064, (1980)). Therefore, in order to separate self-aggregated and degraded material from the preserved protein, the delipidized, reduced, and carboxymethylated ApoB-100 was electrophoresed on a polyacrylamide gel containing 8 M urea. Coomassie blue staining of the urea-polyacrylamide gel was cut out immediately after the completion of electrophoresis and subcutaneously injected ***(while still in the gel)*** [emphasis added] into mice without further manipulation of addition or adjutants."

It is noted that the written description in these passages directed to the apolipoprotein immunogen ApoB-100 do not convey conception of: (a) the subgenus of solubilization with a reducing or denaturing agent as is instantly claimed; (b) removal of all self-aggregated and degraded material (i.e. free from self-aggregated and degraded material) by any means;

(c) soluble lipoprotein (LDL, HDL or VLDL) as an immunizing material; (d) generic immunization with a apolipoprotein that is delipidated, reduced, carboxymethylated and solubilized with a reducing or denaturing agent that is free from aggregates and degradation products and (e) polyclonal antibodies. The relied upon passages still does not support the claimed immunogen or the new subgenus of solubilization. As to point (a) the cited passages of the specification do not convey the subgenus means of solubilization as is now claimed. The only order provided by this passage is that the purification by electrophoration in polyacrylamide gels occurred subsequent to solubilization, delipidation, reduction and carboxymethylation. Moreover, it is the soluble Apo B-100 that is reduced. This passage conveys reduction as a separate process from solubilization. The passage does not specify how the ApoB-100 was solubilized and thus the amendment to provide solubilization with a reducing or denaturing agent provides a new subgenus of agents that is not supported by the original written description and is therefore considered new matter. The recitation of the genus of solubilization does not provide written descriptive support for more narrowly claiming solubilization by a reducing or denaturing agent. This new subgenus of solubilizing agents/methods has no conception in the specification as originally filed. Moreover, to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Appellant was in possession of the invention and that the invention, in that context, is whatever is now claimed. As to point (b) applicants argue that the free of all

self aggregated and degraded material is presumably the result obtained using polyacrylamide gel electrophoresis on page 47. This is not persuasive. Electrophoresis may or may not remove all self aggregated and degraded material. Appellants are presumably relying upon an putative inherent property of a particular process, yet that process limitation is not in the claim. Moreover, presumption is not a showing of inherency. The inserted property, must necessarily flow from the process of the specification. Moreover, with respect to Appellants opinion, the methods of purification of page 42-43 rely upon antibody binding and as such do not, and can not, discriminate between the degraded and aggregated apolipoproteins as opposed to that which is not degraded and aggregated. The generic teachings of immunoaffinity purification will not distinguish these characteristics. The antibodies of the art do not distinguish based upon size and degradation and bind all forms of the apolipoprotein. Appellants' opinion is unsubstantiated and contrary to general scientific teachings in regard to immunoaffinity purification. As to point (c), neither the passage at page 27, nor page 47 provides for conception of a lipoprotein so processed as an immunogen, nor how to utilize gels to remover all self aggregated and degraded from the lipoproteins (LDL, HDL or VLDL). The treatment regimen would destroy the lipoprotein as defined by the art. No purification of a lipoprotein free of self aggregated and degraded material can be made. The specification provides no written description of how to purify lipoproteins so treated. The teachings of the specification are limited to purification of the apolipoprotein components

of the lipoprotein and specific to ApoB-100. As such, the amendment of the claims to recite lipoproteins are processed and purified is deemed new matter. As to point (d), the immunogen used in this specification was not solubilized and reduced. At page 47, the specification teaches that the animal was immunized as "The most prominently stained band in the urea- containing polyacrylamide gel was cut out immediately after completion of electrophoresis and subcutaneously injected (while still in gel) into mice without further manipulation of addition or adjutants". As such, the immunogen of the specification was not administered in a solubilized and reduced form as now claimed. Solubilized by means of convention for proteins is in dissolved in fluid. Secondly, there is no indication in the written description that the polyacrylamide/urea gel used to purify the apolipoprotein and gel used to immunize the animal contained any reducing agent. As such, there is no written description basis for claiming that the immunogen was "reduced" or "solubilized" at the time of immunization as is instantly claimed. Moreover, the passage at pages at page 27 and 47 indicates that reduction was performed before processing to remove self-aggregated and degraded material and that the starting material was a "solubilized" apolipoprotein. Moreover, solubilization as set forth by references in the specification and by art accepted convention, does not include polyacrylamide/urea gel electrophoresis as a means for solubilization. By no means can injection in a polyacrylamide/urea gel be considered "solubilized" as set forth in the claims. Lee et al of record (Biochim. Biophys. Acta, 666:133-146, 1981) sets conventional solubility definition in this art "A test of true

solubility was made by centrifuging the solution at 12,000 xg for 30 minutes in an Eppendorf centrifuge 3200. No precipitate of gel formation was observed. " (see page 136, second full paragraph). Moreover, the specification at page 47 defines the polyacrylamide/urea gel as a purification step and not a solubilization step and further does not state that the polyacrylamide/urea gel was in fact a reducing gel. As such, the immunogen set forth in the specification is neither reduced nor solubilized as is now claimed. As such, Applicants are mixing and matching concepts and method steps to arrive at a method of using an immunogen and method *per se* that has no written description support in the specification as originally filed. As to point (e), the passages are devoid of any mention of polyclonal antibodies and as such is considered new matter.

(11) Response to Argument

Appellants argue that page 37, lines 8-19, line 30 to page 38, line 2, lines 17-25 generally convey Appellants had conceived claim 48. This is not persuasive, page 37, lines 8-19 does not recites the passage quoted by Appellants. However, it is noted that page 27 lines 8-19 does recite the relied upon passage. "To obtain an anti-LDL MAb whose binding to LDL particles is not dependent on variations in LDL composition and/or conformation, mice were immunized with soluble ApoB-100 which had been delipidized, reduced, carboxymethylated and, purified by electrophoration in polyacrylamide gels containing 8 M urea (Lee, D. M. et al, Biochim. Biophys. Acta, 666:133-146(1981)). Immunization with such

delipidized, soluble, reduced, carboxymethylated, and electrophoretically purified Apo B-100 has not been previously reported." This passage only provides support for immunization with the apolipoprotein ApoB-100 and not immunization with any other apolipoprotein, nor does it convey immunization with lipoproteins or denaturation. What is does convey is that the method of immunization with Apolipoprotein B-100 as specifically recited can generate monoclonal antibodies that bind LDL in a specific manner and lack cross-reactivity with other lipoproteins. As such, conception of immunization with lipoproteins or other apolipoprotein is not conceived and would not be recognized by one of skill in the art because lipoproteins are a composition containing different lipids and apolipoproteins. Appellant specifically acknowledges the distinction of the structure of lipoproteins versus apolipoproteins yet does not resolve this issue in the claims. When you delipidate a lipoprotein, all that is left is the apolipoprotein, so in no circumstance does this passage convey immunization with lipoprotein. The skilled artisan recognizes that certain lipoproteins have more than one different apolipoprotein and as can immunization with such can not generate a specific antibody as claimed. Therefore, the skilled artisan would not recognize that such a procedure as set forth in the specification would be generically applicable. As such, this passage does not support immunization with lipoproteins or the particular combination of steps with apolipoproteins or ApoB-100. Appellants also apparently indicate support for making other antibodies at page 37 line 30 to page 38, line 2. Page 37, line 30 to page 38 line 2 recites "apolipoprotein in the blood

sample. Alternatively, the dipstick can fist be incubated with a blood sample for 2 to 5 minutes to bind the apolipoprotein and then washed and immersed into the solution of the MAb-enzyme complex for 10 minute at room temperature. After additional washing, the dipstick is immersed into a solution of chromogenic substrate and stained as explained above. These relied upon passages in the Brief do not support the claimed invention in that they are drawn to methods of using an antibody and therefore speak to the issue of record. If Appellants were referencing page 27, line 30 to page 28 line 2, this passage recites "Chylomicrons are not recognized by HB3cB3 because they lack Apo B-100. The HB3cB3 Mab, and LDL-binding fragments derived therefore, can be used as an LDL-specific binding molecule in all of the compositions and method described herein because of its specificity for LDL and lack of cross-reactivity with other lipoproteins. Antibodies to Apo A-I. Two Mabs raised against apolipoprotein A-I.." These passage also do not support the generic method as now claimed and is specific to the HB3cB3 monoclonal antibody referenced therein. This passage does not support conception of the generic method now claimed. Passages on page 28, lines 1-page 29, line 3 do not support the claimed methods because they specifically reference antibodies made by different methods in the art as clearly shown by the cited references, references which are of record in this Application. For example, the antibodies to ApoA-II on page 28 were produced using purified Apo A-II as an immunogen and the anti-Apo AII Mab, CdB5 is described by Koren, e. et al Aterioscleroses, 6:521(a) (1986); Alaupovic, P. et al., J. Lipid

Research., 32:9-19 (1991)). These antibodies were clearly produced by different immunization methods and can not support conception of the breadth of the now claimed methods. Appellants also argue that the specification describes other antibodies that are lipid independent (page 28, lines 1-16). This is not persuasive, the specification merely states that they were raised against apolipoprotein A-1 and does not convey by written description that the antibodies were made by the same methods described therein for ApoB-100. As such, these other antibodies do not support conception by way of written description of the method now claimed. Appellants argue that Example 2 on page 47 (misquoted as page 62 in the Brief) demonstrates reduction to practice of the claimed invention. This is not persuasive, Example 2 does not support reduction to practice of the claimed invention. The example is limited to specific a monoclonal antibody using a specific procedure. This passage does not mention denaturing agents in the process, does not provide for immunization of soluble material as claimed, nor does it conceive of any means of removal of self aggregated and degraded material of ApoB-100, nor does it support immunization with a soluble lipoprotein. The reference to degredation and aggregation is specific to ApoB-100 and is removed by a specific method. No contemplation of other means is set forth. Importantly, the ApoB-100 which is immunized is "The most prominently stained band in the urea-containing polyacrylamide gel was cut out and immediately after the completion of electrophoresis and subcutaneously injected (while still in the gel) into mice without further manipulation or addition of adjuvants."

Therefore, it is clear from this passage that no soluble ApoB-100 protein was injected, nor reduced to practice. There is no conception of immunization with other apolipoproteins or lipoproteins in these passages. Appellants argue that immunization of an animal with an antigen will always produce polyclonal antibodies. This is not persuasive, the claim requires antibodies that react with the lipoprotein independently of lipid content and conformation of the lipoprotein and this passage provides for only anti-ApoB100 monoclonal antibodies that do so. There is no conception that anti-ApoB-100 polyclonal antibodies could be produced using the method. There is no conception of generic antibodies using the specifics of Example 2.

Appellants argue the legal standard for written description and indicate that the law has long allowed Applicant to claim all that he is entitled to, not forcing to limit his claims to a specific example, if other means for achieving the same step would be know to those skilled in the art and would not require undue experimentation. Undue experimentation is not the issue here. Written description of the claimed invention is the issue. Appellants reiterate that written description has been determined to be a separate fact based legal analysis and cites *Amgen Inc. v. Hoeschst Marion Roussel, Inc. and Trankayotic Therapies*, Inc 314 F3d 1313, 65 USPQ2d 1385, (Fed. Cir. 2003) which cites *Vas-Cath Inc. v Mahukar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written

description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). In this case, the written description does not account the invention in such detail to establish that as of the filing date sought they were in possession of the generic invention now claimed. Appellants characterization of the invention and this particular immunization process in general, as critical thereto, is not found in the specification. Applicants own specification argues against this with the statement "Immunization with such delipidized, soluble, reduced, carboxymethylated, and electrophortically purified Apo B-100 has not been previously reported." (page 27, lines13-16) which indiactes that at the time of filing the concept of immunization was directed to ApoB-100 and directed to ApoB-100. Further, originally filed claim provides for conception of any generic immunization claim as originally filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc.., 41 USPQ2d 1961 (Fed. Cir. 1977). Appellants had no conception of this method as is now claimed. The courts have decided similar issues with respect to disclosure of a single species and attempts to later claim a broad genus. For example, in *In re East and Harmon* (CCPA) 181 USPQ 716 (May 9, 1994) the claims of a reissue application were drawn to new matter since they broadly recite genus of "carrier particles" which is not disclosed in original patent, which discloses only subgenus of "magnetic carrier particles" and species

of "iron, ferrites, nickel, and cobalt" carrier particles. Similarly herein, Appellants broadly recite methods using any assortment of method steps using any assortment of apolipoprotein immunogens and have no conception of the generic method as is now claimed. Appellants did not convey by written description in such a manner as to define the invention as is now broadly claimed. The relied upon passages do not allow the skilled artisan to recognize that the inventors had invented what is now claimed. In contrast to Appellants assertions, the teachings of the application are narrow drawn to specific steps and immunization with particular immunogens prepared by a particular process that was deemed to be not reported for the particular immunogen ApoB-100. This does not convey conception of the broad genus method now claimed. This passage doe not convey polyclonal antibodies nor how to screen for such. In contrast to Appellants assertions, reliance on the recited passages do not provide conception for the genus claim now presented for all the reasons previously made of record and arguments set forth herein. The courts have indicated that if the written description does not use precisely the same terms used in a claim, the question is whether the specification directs or guides one skilled in the art to the subject matter now claimed (see *Fujikawa v. Wattanasi*, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996). This specification does not provide such direction and guidance to the generic method as now claimed for the specific reasons (a)-(e) and those set forth *supra*.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,
Patricia A. Duffy
Primary Examiner
Art Unit 1645

Patricia A. Duffy, Ph.D.
March 21, 2004

Conferees
Lynette Smith, SPE AU 1645

L. F. Smith
LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
Conferee

Brenda Brumback, SPE AU 1654

Brenda Brumback
BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
Conferee

PATREA L. PABST
HOLLAND & KNIGHT LLP
SUITE 2000, ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET, N.E.
ATLANTA, GA 30309-3400